REMARKS

Claims 12 and 14-17 have been canceled and Claims 21-63 have been added to the application. The subject matter of Claims 12 is now claimed in Claims 29-31, and the subject matter of Claim 14, 15, 16 and 17 is now claimed in Claims 37, 59, 46 and 62, respectively.

Support for Claims 21 and 22 is found, for example, at page 4, lines 10-15.

Support for Claim 23 is found, for example, at page 3, lines 3-6.

Support for Claims 24 and 25 is found, for example, at page 15, lines 1-8.

Support for Claims 26-34 is found, for example, at page 14, lines 6-9.

Support for Claims 35-40 is found, for example, at page 15, lines 1-8, and page 16, lines 8-15.

Support for Claims 41-55 is found, for example, at page 15, lines 1-8 and 16-23.

Support for Claims 56 and 57 is found, for example, at page 4, lines 1-9.

Support for Claims 58-60 is found, for example, at page 16, lines 16-18.

Support for Claims 61-63 is found, for example, at page 15, line 24 through page 16, line 7.

The new claims are supported by the application as originally filed. Therefore, this Amendment adds no new matter. Further remarks are presented below with reference to the numbered paragraphs of the Office Action.

Paragraph 2. Rejection of Claims 5, 10 and 18 Under 35 U.S.C. § 112, First Paragraph

Claims 5, 10 and 18 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that Claims 5 and 10, which recite "disease characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation," reach out to as yet unidentified diseases which are not described in the specification. The Examiner further states that the method of antagonizing a C-C Chemokine Receptor 1, as recited in Claim 18, reaches out to as yet unidentified diseases/conditions/activities which are not described in the application.

An application contains adequate written description of the claimed subject matter if the disclosure of that patent application conveys with reasonable clarity to those skilled in the art, that Applicants were in possession of the claimed invention at the time the application was filed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555; 19 USPQ2d 1111 (Fed. Cir. 1991). Possession of the invention can be shown by "describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." (MPEP § 2163 at 2100-165, right column (8th ed., Rev.2, May 2003).) The description need only describe in detail that which is new or not conventional." (Id. at 2100-170, left column.) When a genus is claimed, the written description requirement can be satisfied by sufficient description of a representative number of species within the genus. (Id. at 2100-175, left column.) Disclosure of a representative number of species depends on whether one skilled in the are would recognize that the Applicant was in possession of the common attributes or features of the members of the genus. (Id.)

The Examiner appears to have rejected the claims because she considers the claims to be overly broad. However, an application does not fail to satisfy the written description requirement merely because of the breadth of the claims. The Examiner has not provided reasons why a person skilled in the art at the time the application was filed would not have recognized that Applicants were in possession of the claimed invention, and therefore, has not established a *prima facie* case. (MPEP § 2163(III)(A).)

The specification contains adequate written description of the subject matter of Claims 5, 10 and 18, because the person of skill in the art at the time the application was filed would have concluded that Applicants were in possession of the claimed subject matter.

Claims 5 and 10 recite that the disease is "characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation." The quoted phrase is defined in the specification starting at page 14, which teaches:

> As used herein "pathogenic leukocyte recruitment, activation or recruitment and activation" refers to leukocyte recruitment (*e.g.*, accumulation of leukocytes at a sight of inflammation or injury) and/or activation *(e.g.*, physiologic state in which leukocytes perform effector functions) that contributes to the conditions, processes or results of the disease or disorder to be treated. For example, in a subject afflicted with multiple sclerosis, recruitment and/or activation of T cells in

the central nervous system is considered "pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation," because recruited and activated T cells contribute to the demyelination characteristic of that disease. Similarly, in a subject afflicted with rheumatoid arthritis, recruitment and/or activation of T cells in joints (*e.g.*, synovial tissue or fluid) is considered "pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation," because recruited and activated T cells contribute to the tissue destruction characteristic of rheumatoid arthritis.

Diseases and disorders characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation that can be treated according to the methods described herein include, for example, acute and chronic inflammatory disorders characterized by the presence of CCL2 (MCP-1) CCL3 (MIP-1α), CCL4 (MIP-1β), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL14 (HCC-1), CCL15 (Lkn-1) and/or CCL23 (MPIF-1) responsive cells, such as T cells, monocytes or eosinophils. Such diseases or disorders include, but are not limited to, inflammatory arthritis (*e.g.*, rheumatoid arthritis), inflammatory demyelinating disease (*e.g.*, multiple sclerosis), atherosclerosis, arteriosclerosis, restenosis, ischemia/reperfusion injury, diabetes mellitus (*e.g.*, type 1 diabetes mellitus), psoriasis, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, rejection (acute or chronic) of transplanted organs and tissues (*e.g.*, acute allograft rejection, chronic allograft rejection), graft versus host disease, as well as allergies and asthma. Other diseases associated with aberrant leukocyte recruitment and/or activation which can be treated (including prophylactic treatments) with the methods disclosed herein are inflammatory diseases associated with viral (*e.g.*, Human Immunodeficiency Virus (HIV)), bacterial or fungal infection, such as, AIDS associated encephalitis, AIDS related maculopapular skin eruption, AIDS related interstitial pneumonia, AIDS related enteropathy, AIDS related periportal hepatic inflammation and AIDS related glomerulo nephritis. The method comprises administering to the subject in need of treatment an effective amount of a compound (*i.e.*, one or more compounds) described herein.

As used herein "inflammatory demyelinating disease" refers to acute and chronic inflammatory diseases characterized by demyelination of central nervous system tissue. The inflammatory demyelinating disease can be an acute inflammatory demyelinating disease, for example, acute disseminated encephalomyelitis, Guillain-Barre syndrome or acute hemorrhagic leukoencephalitis. In other embodiments, the inflammatory demyelinating disease can be a chronic inflammatory demyelinating disease, for example, multiple sclerosis, chronic inflammatory demyelinating polyradiculoneuropathy. ...

> As used herein, "inflammatory arthritis" refers to those diseases of joints where the immune system is causing or exacerbating inflammation in the joint, and includes rheumatoid arthritis, juvenile rheumatoid arthritis and spondyloarthropathies, such as ankylosing spondylitis, reactive arthritis, Reiter's syndrome, psoriatic arthritis, psoriatic spondylitis, enteropathic arthritis, enteropathic spondylitis, juvenile-onset spondyloarthropathy and undifferentiated spondyloarthropathy. Inflammatory arthritis is generally characterized by infiltration of the synovial tissue and/or synovial fluid by leukocytes.

(Specification at page 14, line 10 through page 15, line 23.)

Applicants have claimed their invention by describing the patho-physiological characteristics of the disease or condition to be treated. These characteristics, *e.g.*, leukocyte recruitment and/or activation, are well-known characteristic of acute and chronic inflammatory diseases, which are commonly used by clinicians to diagnose and monitor therapy of such diseases. Because the recited patho-physiological characteristics are well-know, further description of the disease to be treated is not needed to meet the written description requirement. The person of ordinary skill in the art would immediately appreciate if a newly discovered disease or disorder were "characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation," because these are common and well-known characteristics of inflammatory disease. If a newly discovered disease were characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation, the person of ordinary skill in the art would consider the claimed methods to be suitable for treating the disease. For this reason alone, the specification provides adequate written description of the subject matter of Claims 5 and 10.

In addition, Applicants have disclosed numerous examples of species of diseases that fall within the genus of diseases that characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogenic leukocyte recruitment and activation. (Specification at page 14, line 10 through page 15, line 23, reproduced above.) The disclosed species are sufficient to show that Applicants were in possession of the claimed genus because the pathological mechanism underlying each of the disclosed species involve aberrant leukocyte recruitment and/or activation. Accordingly, the person skilled in the art at the time the application was filed

would have recognized that Applicants were in possession of the common attributes or features of the members of the genus.

Similarly, the specification contains adequate written description of the subject matter of Claim 19 which recites "antagonizing a C-C Chemokine Receptor 1." Again, at the time the application was filed, functions of C-C Chemokine Receptor 1 (CCR1) which could be antagonized by the claimed method were well-known in the art. In addition, Applicants teach:

> The antagonist compounds can inhibit binding of a ligand (*e.g.*, a chemokine ligand such as CCL2 (MCP-1) CCL3 (MIP-1α), CCL4 (MIP-1β), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL14 (HCC-1), CCL15 (Lkn-1), CCL23 (MPIF-1)) to CCR1. Accordingly, processes or cellular responses mediated by the binding of a chemokine to CCR1 can be inhibited (reduced or prevented, in whole or in part), including leukocyte migration, integrin activation, transient increases in the concentration of intracellular free calcium $[Ca^{++}]_i$, and/or granule release of proinflammatory mediators.

(Specification at page 4, lines 1-9.)

The specification provides further written description for the subject matter of these claims by disclosing the results of binding assays and an *in vivo* guinea pig neutrophil recruitment assay (Table at page 32) which exemplify the claimed method of antagonizing a CCR1.

Based on the teachings and exemplification of the specification and the knowledge in the art at the time the application was filed, the person of skill in the art at the time the application was filed would have concluded that Applicants were in possession of the subject matter of Claims 5, 10 and 19. Accordingly the specification provides adequate written description of the subject matter of these claims.

Reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 3. Rejection of Claims 5, 10 and 18 Under 35 U.S.C. § 112, First Paragraph

Claims 5, 10 and 18 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner states that the scope of the claims is not commensurate with the objective enablement, especially in view of the absence of written

description of as yet unidentified diseases characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogen leukocyte recruitment and activation; and in view of the absence of written description of as yet unidentified conditions/activities/disorders which antagonizing CCR1 reaches out to.

The Examiner further states that claims directed to antagonizing CCR1 would have no practical utility unless antagonizing CCR1 and treatment of inflammatory disease are inexorably linked. It is noted that the Examiner has not cited to any legal authority, or provided reasoning, that supports this assertion. The Examiner also states that the claims embrace any degree of antagonism of the CCR1, which may or may not be linked to the treatment of inflammatory disease.

Claims 5, 10 and 18 are supported by adequate written description for the reasons stated above.

It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

The subject matter of Claims 5, 10 and 18 is enabled because the person skilled in the art could practice the claimed methods without undue experimentation. The specification teaches how to make the compounds, and the claims recite that an effective amount is administered. The specification provides sufficient guidance to allow a person skilled in the art (*e.g.*, a skilled clinician) to practice the claimed method, including guidance as to dosing and modes of administration. (Specification, at page 12, lines 14-15, and page 16, line 23 *et seq.*)

With respect to Claims 5 and 10, as discussed above, it is well within the skill of a skilled clinician to diagnose and treat diseases or disorders characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogen leukocyte recruitment and activation, because these are well-known characteristics of acute and chronic inflammatory conditions. If, as the Examiner postulates, a new disease emerges, it would not require undue experimentation

for a person skilled in the art to determine if the new disease is characterized by pathogenic leukocyte recruitment, pathogenic leukocyte activation or pathogen leukocyte recruitment and activation. Suitable methods for assessing these characteristics are commonly used in clinical laboratories and are considered routine in the art.

With respect to Claim 18, the Examiner's concerns regarding antagonism being inexorably linked to treatment of inflammatory disease are misplaced. Claim 18 does not recite "treatment of an inflammatory disease." The claimed method of antagonizing a CCR1 has practical utility and can be practiced without undue experimentation. For example, the specification discloses an example in which various doses of compounds were administered to guinea pigs, CCR1-dependent neutrophil recruitment was induced by injecting the CCR1 ligand MPI-1α locally into the skin, and neutrophil recruitment to the injection site was measured. (Specification at Example 5, page 30.) The administration of different amounts of compound resulted in different levels of antagonism of CCR1 and inhibition of neutrophil recruitment to the injection sites. Because of the different levels of antagonism, and Effective Dose 50 (ED50) could be determined. (Specification at the Table, page 32.) Thus, achieving various degrees of antagonism of CCR1 has practical utility, for example, in determining ED50 or other measures of bioavailability and/or efficacy of compounds, formulations and/or routes of administration. Moreover, achieving a desired level of antagonism of CCR1 would not require undue experimentation as demonstrated by the actual reduction to practice disclosed in Example 5 and the Table of the specification.

Given the guidance provided in the specification and the level of skill in the art, it would not require undue experimentation to practice the methods of Claims 5, 10 or 18. Therefore, the enablement requirement of 25 U.S.C. § 112 is satisfied.

Reconsideration and withdrawal of the rejection are respectfully requested.

Paragraph 4. Rejection of Claims 1-19 Under 35 U.S.C. § 103(a)

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as being obvious over Luly *et al.* (U.S. 2002/0169155). The Examiner states that Luly *et al.* discloses a generic formula that encompasses the claimed compounds, and further states that Luly *et al.* discloses Example 438 which has a 3-methyl on the piperidinyl. (Office Action at page 4.) Applicants' claimed

compounds have a 3,3-*gem*-dimethyl on the piperidinyl. The Examiner further states that Luly *et al.* disclose a compound (Example 443) which contains a 3,3-*gem*-dimethyl-piperidinyl. (Id.) The Examiner concludes that the claims are obvious because the person of ordinary skill in the art would have been motivated to replace the 3-methyl-piperidinyl on Example 438 of Luly *et al.* with 3,3-*gem*-dimethyl-piperidinyl with a reasonable expectation of success of obtaining additional compounds for treating inflammatory diseases, because Luly *et al.* teaches that any species within the disclosed generic formula would be an effective CCR1 antagonist. (Id.)

A finding that the claimed invention is obvious under 35 U.S.C. § 103 requires that (1) "the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process"; and (2) that "the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. (emphasis added). It is an axiom of patent law that, "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." In re Petering, 301 F.2d 993, 1002, 133 USPQ 275 (C.C.P.A. 1962); In re Jones, 958 F.2d 347, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992); In re Baird, 16 F.3d 380, 29 USPQ2d 1550, 1552 (Fed. Cir.1994). To support a *prima facie* case of obviousness, the prior art must contain a teaching which suggests or provides motivation to select the claimed compound or subgenus from the disclosed genus. In re Jones, at 1943-1944. Further, that the disclosure of a reference can be modified does not render the result of the modification obvious unless the prior art suggest the desirability of the modification. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Claims 1-19 are not obvious over Luly *et al.*, and a *prima facie* case has not been established, because the reference does not suggest or provide motivation to select and combine the particular variables, from the vast number of possibilities encompassed by the generic formula, necessary to arrive at the claimed compounds. The combination of features that the Examiner selected and relies on is not specifically disclosed by Luly *et al.*, and Luly *et al.*

provides no teaching that reasonably suggests or provides motivation to select the particular combination from the vast number of possible combinations encompassed by the disclosed generic formulae. There is no suggestion or motivation in the teachings of Luly *et al.* to combine the 3,3-*gem*-dimethyl piperidine feature, which appears in only one of about 455 exemplary compounds, with the independent R^{40} = -COOH feature, which appears in only about one percent of the exemplary compounds. Luly *et al.* does not exemplify any compounds that contain this combination, does not disclose a subgenus in which each species contains the combination, does not teach that the combination is preferred, and does not teach that the combination provides any benefits relative to the broad genus. Accordingly, as discussed below, based on the full teachings and examples of Luly *et al.,* the person of ordinary skill in the art would not have been motivated to select this combination of features, or even the individual features, form the vast number of disclosed possibilities. Accordingly, a *prima facie* case of obviousness has not been established because, Luly *et al.* does not contain a teaching which suggests or provides motivation to select the claimed compounds from the disclosed genus. (See, In re Jones, at 1943-1944.)

In addition, the Examiner's view of the teachings of Luly *et al.* appears to have been colored by Applicants' disclosure of the claimed compounds and their advantages (*e.g.*, greater bioavailability and efficacy) compared to structurally related compounds. Thus, the rejection is based upon impermissible hindsight reconstruction.

A. Teachings of Luly *et al.*

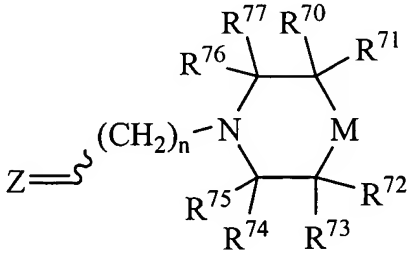
i. The -COOH R^{40} substituent

Luly *et al.* do not suggest that a -COOH substituent at R^{40} should be selected. Luly *et al.* disclose a large genus of compounds and present the structures of about 455 exemplary compounds. Only 5 of the exemplary compounds contain a -COOH substituent on the tricyclic moiety at the position corresponding to R^{40} in the formula of Luly *et al.* (Luly *et al.*, Formula VI at page 5, and Figures 1-20). In contrast about 91 exemplary compounds contain a -O-CH_3 substituent at this position, and about 20 exemplary compounds contain a -OH substituent at this position. (Luly *et al.* at Figures 1-20.) In addition, there is nothing in the reference that teaches or reasonably suggests that compounds containing a -COOH substituent on the tricyclic moiety at R^{40} have any advantages over any other compound encompassed by the vast general formula of

Luly *et al.* Accordingly, there is no suggestion or motivation to select the -COOH substituent at R^{40} from the vast number of possibilities. In fact, it appears that the person of ordinary skill in the art would have considered Luly *et al.* to suggest that -O-CH_3 or -OH should be selected for R^{40}, based on the large number of exemplary compounds that contain these groups.

ii. The 3,3-*gem*-dimethyl piperidinyl moiety

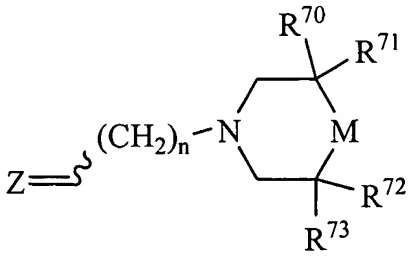
Luly *et al.* do not suggest that a 3,3-*gem*-dimethyl piperidinyl should be selected. Luly *et al.* disclose generic formula VIII, which encompasses compounds that contain substituents at the two and/or three position of a piperidinyl or piperazinyl moiety, or at the two, three, seven and/or eight position of a 4,6-dioxazacanyl or 4-oxazacanyl moiety. (Luly *et al.* at page 7.)



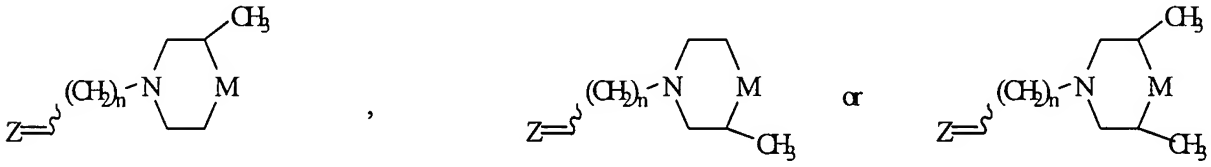
(VIII)

Luly *et al.* teach that in Formula VIII, M is $>NR^2$, CR^1R^2, -O-CR^1R^2-O- or -CH_2-CR^1R^2-O-; and R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} are independently -H, -OH, -N_3, a halogen, an aliphatic group, a substituted aliphatic group, an aminoalkyl group, -O-(aliphatic group), -O-(substituted aliphatic group), -SH, -S-(aliphatic group), -S-(substituted aliphatic group), -OC(O)-(aliphatic group), -O-C(O)-(substituted aliphatic group), -C(O)O-(aliphatic group), -C(O)O-(substituted aliphatic group), -COOH, -CN, -CO-NR^3R^4, -NR^3R^4, an acyl group, a substituted acyl group, a benzyl group, a substituted benzyl group, a non-aromatic heterocyclic group, a substituted non-aromatic heterocyclic group, -O-(substituted or unsubstituted aromatic group), or any two of R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} taken together with the atoms to which they are bonded form a three to eight membered ring. (Id.) This generic formula encompasses a vast number of compounds.

Luly *et al.* further teaches that in certain embodiments R^{74}, R^{75}, R^{76} and R^{77} are -H, and at least one of R^{70}, R^{71}, R^{72} and R^{73} is an aliphatic group or a substituted aliphatic group. (Id.) Accordingly, the compound has the formula:



Luly *et al.* further teach that in more particular embodiments, R^{70}, R^{73}, R^{74}, R^{75}, R^{76} and R^{77} are -H, and at least one of R^{71} and R^{72} is $-CH_3$. (Id.) In such embodiments, the compound can contain a 3- methyl or 3,3-dimethyl piperidinyl or piperazinyl, or a 3- methyl or 3,7-dimethyl 4,6-dioxazacanyl or 4-oxazacanyl that has the formula



It is noted that Luly *et al.* further disclose a formula encompassing a sub-genus of compounds that contain a 3,5-dimethyl piperidinyl (Formula I-f, Figure 16).

In addition, of the 455 exemplary compounds disclosed by Luly *et al.* only 9 contain a substituent that corresponds to any of R^{70}-R^{77} in formula VIII. Of these, one compound contains a 2,5-dimethyl piperidinyl (Example 221), six contain a 3-methyl piperidinyl (Examples 434-438 and 441), one contains a 3-hydroxy piperidinyl (Example 442), and one contains a 3,3-*gem*-dimethyl piperidinyl (Example 443).

In addition, there is nothing in the reference that teaches or reasonably suggests that compounds containing a 3-methyl piperidinyl, 3,5-dimethyl piperidinyl or 3,3-*gem*-dimethyl piperidinyl have any advantages over any other compound encompassed by the vast general

formula of Luly *et al.* Accordingly, there is no suggestion or motivation to select a 3,3-*gem*-dimethyl piperidinyl moiety from the vast number of possibilities encompassed by the generic formula of Luly *et al.* In fact, based on the exemplary compounds, descriptions of particular embodiments, and the disclosure of a formula encompassing a subgenus of compounds that contain a 3,5-dimethyl piperidinyl, it appears, at best, that the person of ordinary skill in the art would have considered Luly *et al.* to suggest that 3-methyl piperidinyl or 3,5-dimethyl piperidinyl could be used.

This view is also supported by the claims of Luly *et al.*, which do not claim compounds that contain a 3,3-*gem*-dimethyl piperidinyl with specificity. For example, independent Claim 24 is drawn to a broad genus of compounds, while dependent Claims 32-34 are drawn to compounds that contain a 3,5-disubstituted piperizinyl or piperidinyl, Claim 35 is drawn to compounds that contain a 3,5 dimethyl piperazinyl or piperidinyl, and Claims 36 and 37 are drawn to compounds that contain a 3-(C_1-C_6 alkyl) piperazinyl or piperidinyl. In addition, Claims 40 and 41 are drawn to compounds that contain a 3-alkyl piperidinyl or 3,5-dialkyl piperidinyl. However, no claims specify that the compound contains a 3,3-*gem*-dimethyl piperidinyl.

In view of the full teachings of Luly *et al.,* including the disclosure of only 9 exemplary compounds (out of 455 disclosed exemplary compounds) that contain a piperidinyl moiety with a substituent that corresponds to any of R^{70}-R^{77} in formula VIII, Luly *et al.* does not reasonable suggest to the person of ordinary skill in the art that such a substituted piperidinyl should be selected. However, even if the Examiner concludes that Luly *et al.* does provide some motivation or suggested to select certain substituted piperidinyl moieties, the person of ordinary skill in the art would have selected 3-methy piperidinyl or 3,5-dimethyl piperidinyl, because the description, examples and claims of Luly *et al.* focus on these moieties. According, Luly *et al.* provide no motivation or suggestion to select a 3,3-*gem*-dimethyl piperidinyl moiety.

iii. The 3,3-*gem*-dimethyl piperidinyl/-COOH combination.

There is nothing in the teachings of Luly *et al.* that suggest or provide motivation to select and combine the 3,3-*gem*-dimethyl piperidinyl feature, which appears in only one of about 455 exemplary compounds, with the independent R^{40} = -COOH feature, which appears in only about one percent of the exemplary compounds. None of the exemplary compounds of Luly *et al.*

contain this combination, Luly *et al.* does not disclose a genus or subgenus in which each species contains the combination, does not disclose a species that contains the combination, does not teach that the combination is preferred, and does not teach that the combination provides any benefits relative to the broad genus.

B. The Rejected Claims Are Not Obvioius Over Luly *et al.*

The full teachings and examples of Luly *et al.* do not suggest or provide motivation for the person of skill in the art to select either the R^{40} = -COOH feature or the 3,3-*gem*-dimethyl piperidinyl feature from the vast number of possibilities encompassed by their general formulae. For this reason alone, the subject claims are not obvious. However, the rejection requires that these distinct features be selected and combined, and there is no suggestion or motivation in Luly *et al.* to combine the features. The reference does not disclose any exemplary compounds that contain both features, does not disclose a genus or subgenus in which each species contains the combination, does not disclose a species that contains the combination, does not teach that the combination is preferred, does not teach that the combination provides any benefits relative to the broad genus, and does not teach or suggest that the combination is desirable. In the absence of such teachings, the claims are not obvious, and a *prima facie* case has not been established, because the person of ordinary skill in the art would not have been motivated to select the combination of features from the enormous number of possible combination encompassed by the generic formulae of Luly *et al.*

Moreover, Applicants' teachings and examples reveal that the claimed compounds provide advantages over structurally related compounds. In particular, Applicants' teach that the claimed compounds have greater bioavailability and efficacy compared to structurally related compounds, and have greater selectivity compared to structurally related compounds when assayed on G protein-coupled receptors and ion channels.

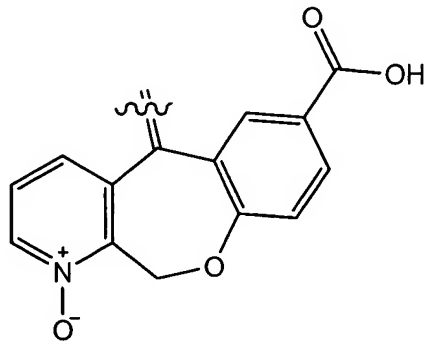
i. Claim 6

Claim 6 is not obvious over Luly *et al.* for the reasons discussed above, and because Claim 6 encompasses compounds that have the stereo chemistry ((*S*)-enantiomer) depicted in the

structural formula presented in the claim. Luly *et al.* does not teach or suggest the claimed (*S*)-enantiomer.

ii. Claim 19

Claim 19 is not obvious for the reasons discussed above, and because the compounds of Claim 19 comprise an Oxa-pyridine containing tricyclic moiety.



Luly *et al.* do not teach or suggest this particular tricyclic moiety.

Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

An Information Disclosure Statement (IDS) was filed on June 16, 2004. Acknowledgment of the information provided in the IDS is requested in the next Office Communication.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Robert H. Underwood

Robert H. Underwood
Registration No. 45,170
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: November 23, 2004